REMARKS/ARGUMENTS

I. Introductory Comments

This reply is in response to the non-final Office Action of September 23, 2003 where all pending claims 16-25 were rejected under 35 U.S.C. §103(a) as assertedly rendered obvious by various references discussed below. Applicants thank Examiner Wang and Supervisory Examiner Padmanabhan for participating in the telephonic interview of November 18, 2003 and for agreeing to reconsider the Applicants' remarks, specifically with regard to the content of previously-submitted declarations of W. James Waldman and Edward S. Mocarski.

II. Subject Matter of Applicants' Claims

Sole independent claim 16 is directed to Applicants' discovery that immunosuppressant leflunomide products inhibit viral replication in infected host cell. Unlike known anti-viral compounds which generally interfere with replication of viral DNA, leflunomide products have been demonstrated by Applicants to interfere with the assembly, in the cell cytoplasm, of viral virion components such as viral DNA-containing nucleocapsids, tegument and external proteins. (*See* particularly Examples 5 and 8c.)

Leflunomide products are thus the only known compounds that possess both immunosuppressant effects and anti-viral effects *in vivo*.

III. Outstanding Rejections

Claims 16, 17, 20, 21, 24 and 25 were rejected under 35 U.S.C. § 103(a) as assertedly rendered obvious by disclosure of Weithmann *et al.*, U.S. Patent No. 5,556,870 (hereafter "Weithmann"); and with respect to Claim 19 in view of Flamand *et al.*, *J. Virol*, 65:5105-5110 (1991) cited as CAPLUS Abstract, AN 1991:581163 (hereafter "Flamand"); and with respect to Claims 23 and 24 in view of Hammer, *AIDS*, 10: supp. 3 (hereafter "Hammer"). It was the Examiner's position in paragraph 4 of the Office Action that the Weithmann reference's disclosure of use of leflunomide (but not its natural metabolite) for inhibiting *in vitro* production of IL-1β in mononuclear cells stimulated with bacterial (*Salmonella*) endotoxin teaches that leflunomide was "known to be useful for treating viral

infection" and that leflunomide is thus a "known anti-viral agent." The Examiner further maintained that, "Since leflunomide is effective against virus through a different mechanism it would have been reasonably expected to be effective against those virus with resistance to anti-viral agents that inhibit viral DNA replication."

Claims 16-20, 24 and 25 were rejected under 35 U.S.C. § 103(a) as assertedly rendered obvious by the disclosures of Coghlan *et al.*, WO 94/24095 (hereafter "Coghlan") in view of McChesney *et al., Transplantation, 57:*1717-1722 (1994) (hereafter, "McChesney") and with respect to Claims 23 and 24 in further view of Hammer. It was the Examiner's position in paragraph 10 of the Office Action that, based on the disclosures of Coughlan, leflunomide "homolog" products, "are known to be useful for treating or preventing viral infection such as hepatitis and cytomegalovirus infection, particularly, HCMV." *See*, page 4, lines 23-32. It was the Examiner's further position in paragraph 17 of the Office Action that the affirmative claim recitation of "inhibiting viral replication" was somehow a mere statement of "functional limitation" having no significance to patentability given the "well-known ultimate utility (anti-viral) for the compounds."

IV. Grounds for Reconsideration

A. The Section 103(a) Rejection Based on Weithmann, Flamand and Hammer May Properly Be Withdrawn.

Applicants submit that no *prima facie* case of obviousness of the claimed subject matter can properly be made out through application of the primary reference (Weithmann) standing alone or in combination with secondary references (Flamand or Hammer). *See*, W. James Waldman Declaration, previously made of record (hereafter "Waldman Declaration").

Weithmann does not establish that any leflunomide product was known in the art to be useful as an "anti-viral agent" or to be "effective against virus" or to be capable of inhibiting viral replication as claimed by the Applicants. Rather, Weithmann at best *asserts* only that *in vitro* tests of un-metabolized leflunomide (HWA 486) possess activity in modulating the *in vitro* secretion of IL-1β by cells in patients having any number of diseases, including viral infections. (*See* Waldman Declaration, specifically Paragraph 5). There is no teaching in Weithmann that the un-metabolized leflunomide treats the diseases listed, such as

Alzheimer's disease or any viral infections, only that IL-1β secretion might be modulated in patients with such diseases.

Further, the ability of un-metabolized leflunomide to modulate IL-1β secretion was stated to be ineffective with metabolized leflunomide, even though Weithmann states that leflunomide (HWA 486) is rapidly metabolized upon administration to form active metabolite (A771726) (column 1, lines 9-37) and then observes that leflunomide, but not its metabolite, has activity in inhibiting cytokine "synthesis and liberation" (*See* Column 1, lines 45-49, emphasis supplied). Weithmann "demonstrates" *in vitro* an IL-1β reduction effect in a specially-prepared isolated blood cell fraction which was designed with a reduced capacity to metabolize leflunomide (*See* Example 1 and column 3, lines 23-26), but never addressed how to provide the special *in vitro* test conditions *in vivo*, i.e. how to prevent leflunomide from being metabolized promptly upon administration. There is simply no reading of the Weithmann specification or the claim that supports a theory that Weithmann discloses anything other than modulating IL-1β activity with leflunomide products.

In contrast, Applicants exemplify antiviral effects of leflunomide products, including reduction of the viral load in a human, with leflunomide's metabolite, A771726 (*See* particularly Examples 5 and 8C of the Application).

Citing to and quoting from MPEP §716.07, the Examiner has taken the position in paragraph 14 of the Office Action that the content of the Waldman Declaration should be ignored in its entirety because it constitutes a "non-probative" attack on operability of the Weithmann, *et al.* reference. This position is erroneous for a number of reasons.

First of all, the Waldman Declaration does not simply address the Weithmann, *et al.* reference. Starting at paragraph 6, Dr. Waldman addresses the profoundly probative issue of whether a skilled worker would, at the time of the invention, expect any anti-inflammatory/immunosuppressive agent to possess anti-viral activity when, as documented in the Tab A literature references attached thereto, other immunosuppressive drugs were known to enhance prospects for development of viral infections. In paragraph 8 of his Declaration, Dr. Waldman compares *in vivo* anti-viral effects (on rats) of leflunomide and two other immunosuppressants commonly employed to treat transplant patients, cyclosporine (CsA) and FK506. Dr. Waldman advises in paragraph 9 that the structurally distinct compound, mycophenolate mofetil (MMF), a known potentiator of certain anti-viral drugs, has no anti-

viral effect on its own and may even be ill-suited for combined therapy of certain viral infections. Finally, in paragraphs 10-11, Dr. Waldman addresses the possibility that the known tyrosine kinase inhibitor activity of leflunomide might fairly suggest anti-viral activity. He tested the effects of structurally dissimilar (to leflunomide) protein tyrosine kinase inhibitors (tyrophostins) previously reported in the literature to display anti-viral effects in comparison with leflunomide metabolite and his results (Figure 5) establish that no anti-viral effect could be confirmed for the "leading candidate" tyrophostin (AG17) due to its significant toxicity.

Dr. Waldman's literature review and experimental studies are directly related and probative to the issue of whether the Weithmann reference or any other prior art reference could fairly be maintained to suggest any anti-viral activity for leflunomide products. They may not properly be ignored in assessing patentability of the claimed subject matter.

As for the statements in the Waldman Declaration specifically addressing the Weithmann, *et al.* reference, Applicants respectfully disagree that they simply constitute an attack on "operability" of the reference. Firstly, Applicants are entitled to provide fair, expert comment on what a patent reference actually discloses, whether or not that expert comment has any relevance to operability of the subject matter claimed in the reference. In this instance, Dr. Waldman fairly comments that Weithmann *et al.*, conducted no tests for anti-viral activity and that the test work assertedly performed by Weithmann, *et al.*, [incubating mononuclear cells with various concentrations of leflunomide and bacterial (*Salmonella*) endotoxin under conditions inhibiting formation of leflunomide metabolite and then measuring interleukin-1β following incubation] would not suggest to the skilled worker that Weithmann, *et al.'s* proposed leflunomide treatments constituted "a method known to be useful for treating viral infection." as had been asserted by the Examiner. *See* Waldmann Declaration, paragraph 5. Secondly, to the extent that the highly peculiar experimental procedures adopted by Weithmann, *et al.* to "support" the claimed treatment method subject matter of the patent are conspicuously "non-scientific," they too are proper subjects for fair expert comment by Dr. Waldman, whether or not they have a bearing on operability. Simply put, Weithmann, *et al.* posit that leflunomide will inhibit IL-1β synthesis, but its metabolite will not. The Weithmann, *et al. in vitro* experiments with leflunomide were conducted under experimental conditions which inhibit the rapid, natural conversion of that compound to its

(assertedly inactive) metabolite. It is quite plain that the experiments are of marginal scientific value in predicting success at *in vivo* inhibition of IL-1β synthesis where rapid metabolism of leflunomide cannot be controlled. As noted by the Examiner, the presumption of operability of a patent reference can be rebutted by a preponderance of evidence. Here, the evidence pointed to by Dr. Waldman is all contained in the Weithmann specification which acknowledges rapid metabolism of leflunomide *in vivo* and posits total loss of the desired activity when such metabolism takes place.

Applicants thus maintain that the Waldman Declaration should not have been ignored by the Examiner when determining whether the Weithmann, *et al.* disclosures actually support the joint conclusions that leflunomide was "known to be useful for treating viral infection" and that leflunomide was a "known anti-viral agent." To the contrary, based on the complete exposition of the art and experimental studies carried out by Dr. Waldman, it is clear that no skilled person would read Weithmann, *et al.* as teaching that leflunomide products had anti-viral (replication-inhibiting) properties and that no skilled person would expect that such anti-viral activity could be predicted from the known immunosuppressive or protein tyrosine kinase inhibitory effects of leflunomide products.

It follows that no *prima facie* case of obviousness can be made out through combination of the Weithmann "teachings" with the disclosures of the secondary references Flamand (addressing IL-1β production by virally-infected cells) or Hammer (addressing pyridinyl compounds as anti-retroviral agents) because: (1) the primary Weithmann reference contains no suggestion of the anti-viral properties of leflunomide products as claimed by the Applicants, nor did the knowledge generally available to one of ordinary skill in the art at the time of Applicants' filing suggest the modification of the references or to combine their teachings; (2) there is no reasonable expectation shown in the art for success of using leflunomide products as inhibitors of viral replication as claimed; and (3) the references alone or in combination do not teach all the limitations of the claims.

The lack of a *prima facie* case for obviousness is most conspicuous for the subject matter of claim 24 which addresses use of leflunomide products to inhibit replication of viruses that are resistant to drugs that inhibit viral DNA replication. In order to reach the conclusion of obviousness set out in paragraph 4 of the Office Action, the Examiner has

assumed that the Applicants' disclosure of leflunomide's effects in inhibiting virion assembly is part of the state of the art. It is not.

The foregoing is believed to establish that the outstanding rejection of claims 16, 17, 20, 21, 24 and 25 based on the disclosures of Weithmann, *et al.*, alone or in combination with the cited secondary references, may properly be withdrawn.

B. The Section 103(a) Rejection Based on Coghlan and McChesney May Properly Be Withdrawn.

Applicants respectfully submit that one of ordinary skill in the art would not find the disclosures of the Coghlan reference, alone or in combination with those of McChesney, sufficient to support a *prima facie* case of obviousness for the Applicant's claimed subject matter. Applicants further submit that the Examiner erred in ignoring the claim recitation of "inhibiting viral replication" and in maintaining that anti-viral activity as an "ultimate utility" of leflunomide products was known from the cited references.

Coghlan addresses the synthesis of compounds "having immunomodulatory activity" (page 1, line 6-7). Addressing leflunomide product immunomodulators specifically at page 2, lines 18 *et seq.*, the reference notes that the long half life of the leflunomide metabolite "may hamper treatment of opportunistic infections in immunosuppressed patients." and, if not structurally modified, may provide for "prolonged susceptibility to viral and other infections." The reference is said to provide novel open-ring imoxazole compounds which are immunomodulatory "but which may be found to minimize untoward side effects." (Emphasis added.) The reference then lists disease states assertedly treatable with such structurally modified immunomodulatory agents (page 3, line 1 - page 4, line 30). This list includes virtually every conceivable illness having a direct or indirect immunological component and concludes with reference to a few viral diseases. Not one single scientific publication is cited for a showing of efficacy of leflunomide or structurally related isoxazoles in any of the disease states listed. The sole assay for biological activity (Example 295) is a mixed lymphocyte test, having no connection whatsoever to the assessment of anti-viral activity. Coghlan does not teach that the open-ring isoxazole compounds structurally related to leflunomide products inhibit viral replication or that leflunomide products have such activity. Indeed, Coghlan teaches away from use of leflunomide, and particularly its

metabolite, for treating *any* disease state on grounds that such treatment would *prolong* susceptibility to viral infections.

Likewise, one of ordinary skill in the act would not find McChesney sufficient to support a *prime facie* case of obviousness alone, or in combination with Coghlan. Contrary to the Examiner's assertion, McChesney *et al.* does not teach that leflunomide and A771726 are known to be effective in preventing viral infection. As confirmed in the Declaration of Edward S. Mocarski previously made of record (hereafter "Mocarski Declaration"), the Examiner's position is simply not supported by the reference. McChesney evaluates the immunosuppressive effects of leflunomide alone and in combination with cyclosporine in dogs undergoing kidney allograft transplantation. The only mention in McChesney of viral infection is a statement in the abstract that, "Even at a high dose of 16mg/kg/day no viral or bacterial infections were noted." There is nothing reported in the article to support or explain this statement, which would be necessary in order to attribute the cause for such an observation to the administered drugs (*See* Mocarski Declaration, specifically Paragraph 5). Moreover, it is not surprising that McChesney noted this lack of viral infection. Institutional animal care guidelines (followed by McChesney according to page 1721) require full vaccination of animals (*See* Mocarski Declaration, Paragraph 5).

Because the McChesney reference includes no experimental procedures for assessing antiviral or antibacterial effects of leflunomide, it cannot properly be held to teach the use of leflunomide products for inhibiting viral replication.

Clearly then, the Coghlan and McChesney references, viewed alone or in combination, provide the skilled worker with no hint whatsoever that leflunomide products had been found to be effective in inhibiting viral replication or might be tested for such effects with any reasonable expectation of success. Likewise, there is no suggestion in these references that leflunomide products might inhibit viral replication by a means other than inhibiting DNA replication and therefore useful when treating "drug resistant" virus infections. The outstanding rejection of claims 16-20, 21, 24 and 25 based on these references may properly be withdrawn.

V. Conclusion

The foregoing is believed to establish that claims 16-25 are in condition for allowance and an early notice thereof is solicited.

Dated: December 23, 2003

Respectfully submitted,

By 

Michael F. Borun
Registration No.: 25,447
Pamela L. Cox
Registration No. 51584
MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Drive, Suite 6300
Chicago, Illinois 60606-6357
(312) 474-6300
Attorneys for Applicant